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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/802,332	03/16/2004	Naoki Kimura	14875-040003/C1-806PCT-US	3754

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FISH & RICHARDSON PC
P.O. BOX 1022
MINNEAPOLIS, MN 55440-1022

EXAMINER	
BELYAVSKYI, MICHAIL A	
ART UNIT	**PAPER NUMBER**
1644	

DATE MAILED: 08/29/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/802,332	KIMURA ET AL.	
	Examiner	Art Unit	
	Michail A. Belyavskyi	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 May 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *28-30* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *28-30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. 09/411,722.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *03/16/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's amendment, filed 05/03/04 is acknowledged.

Claims 28-30 are pending.

Claims 28-30 reads on an antibody that specifically binds to a polypeptide having at least 60 % identity to SEQ ID NO:2 are under consideration in the instant application.

2. The specification on page 1, line 4 should be amended to reflect the status of the parent 09/855,266 application.

3. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention *to which the claims are directed.*

4. Acknowledgment is made of applicant's claim for foreign priority under 35 U.S.C. 119(a)-(d). The certified copy has been filed in parent Application No. 09/411,722, filed on 10/01/1999.

5. Applicant's IDS, filed 03/16/04 is acknowledged. A references cited in IDS have been filed in parent Application No. 09/411,722, filed on 10/01/1999.

6. The disclosure is objected to because it contains an embedded hyperlink on page 21, line 34. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

7. 35 U.S.C. §101 states:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

8. Claims 28-30 are rejected under 35 USC 101 because the claimed invention is directed to non-statutory subject matter.

Claims 28-30 , as written, do not sufficiently distinguish over nucleic acids, proteins, cells and antibodies as they exist naturally because the claims do not particularly point out any non-naturally occurring differences between the claimed products and the naturally occurring products. In the absence of the hand of man, the naturally occurring products are considered non-statutory subject matter. *See Diamond v. Chakrabarty*, 447 U.S. 303, 206 USPQ 193 (1980). The claims should be amended to indicate the hand of the inventor, e.g., by insertion of "Isolated" or "Purified" as disclosed on page 14, lines 10-34 of the instant specification. See MPEP 2105.

9. The following is a quotation of the second paragraph of 35 U.S.C. 112.
The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claim 30 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 30 is indefinite, ambiguous and unclear. In is unclear how the polypeptide encoded by a first nucleic acid that hybridizes under stringent conditions to a second nucleic acid consisting of SEQ ID NO:3, induces differentiation of an osteocyte. Nucleic acid hybridization is a process by which the DNA of a gene is detected by its base pairing with a **complementary** sequence on another nucleic acid molecule. Thus, the complementary (antisense) sequence of said first nucleic acid sequence does not encode the polypeptide that induces differentiation of an osteocyte.

11. The following is a quotation of the first paragraph of 35 U.S.C. 112:
The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

12. Claims 28 and 30 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated antibody that specifically binds to a polypeptide consisting of SEQ ID NO:2 does not reasonably provide enablement for: (i) an antibody that specifically binds to a polypeptide having an amino acid sequence at least 60 % identical to SEQ ID NO:2, claimed in claim 28; or (ii) an antibody that specifically binds to a polypeptide encoded by the first nucleic acid that hybridized under stringent conditions to a second nucleic acid consisting of SEQ ID NO:3, recited in claim 30. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The specification does not enable one of skill in the art to practice the invention as claimed without undue experimentation.

The claims as written encompass the genus of antibodies that can specifically bind polypeptides wherein such polypeptides have numerous differences in amino acid sequences.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, limited working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention.

A. Applicant disclosed a novel secretory protein 7F4 of SEQ ID NO:2, encoded by a nucleic acid of SEQ ID NO:3 that can induces differentiation of an osteocyte (see entire Specification, page 3, lines 15-30 and page 6, lines 15-30 in particular). Applicant also disclosed antibody that specifically binds said polypeptide consisting of SEQ ID NO:2 that can be used for purification, detection of said protein or for antibody therapy of bone disorder(see overlapping pages 14 – 15). Applicant has not taught how to make and/or use (i) any isolated antibody that specifically binds to a polypeptide having an amino acid sequence at least 60 % identical to SEQ ID NO:2, claimed in claim 28; or (ii) any antibody that specifically binds to a polypeptide encoded by the first nucleic acid that hybridized under stringent conditions to a second nucleic acid consisting of SEQ ID NO:3, recited in claim 30. The structural and functional characteristics of said polypeptides are not defined in the claim. Applicant has not provided sufficient biochemical information (e.g. structural characteristics, amino acid composition , physicochemical properties, etc) that distinctly identifies *any* polypeptide having an amino acid sequence at least 60 % identical to SEQ ID NO:2, or *any* polypeptide encoded by the first nucleic acid that hybridized under stringent conditions to a second nucleic acid consisting of SEQ ID NO:3, other than a polypeptide consisting of SEQ ID NO:2 that are capable to induces differentiation of an osteocyte. While any "polypeptide having an amino acid sequence at least 60 % identical to SEQ ID NO:2, or *any* polypeptide encoded by the first nucleic acid that hybridized under stringent conditions to a second nucleic acid consisting of SEQ ID NO:3" may have some notion of the activity of the " 7F4 protein of SEQ ID NO:2", claiming biochemical molecules by such properties fails to provide sufficient guidance and direction as to how the skilled artisan can make and use such antigens, to prepare antibody that can be used for purification and detection 7F4 protein of SEQ ID NO:2 or for antibody therapy of bone disorder commensurate in scope with the claimed invention.

Colman *et al.,* in Research in Immunology (145(1):33-36, 1994) teach single amino acid changes in an antigen can effectively abolish antibody antigen binding. Abaza *et al.,* in Journal of Protein Chemistry (11(5):433-444, 1992) teach that single amino acid substitutions outside the antigenic site on a protein effect antibody binding. Further, Lederman *et al* in Molecular Immunology (28:1171-1181, 1991) disclose that a single amino acid substitution in a common

allele ablates binding of a monoclonal antibody (see entire document). Li *et al* in PNAS (77:3211-3214, 1980) disclose that dissociation of immunoreactivity from other biological activities when constructing analogs (see entire document). Moreover, Attwood (Science 2000; 290:471-473) teaches that "[i]t is presumptuous to make functional assignments merely on the basis of some degree of similarity between sequences. Similarly, Skolnick et al. (Trends in Biotech. 2000; 18(1):34-39) teach that the skilled artisan is well aware that assigning functional activities for any particular protein or protein family based upon sequence homology is inaccurate, in part because of the multifunctional nature of proteins (e.g., "Abstract" and "Sequence-based approaches to function prediction", page 34). Moreover, Whisstock et al (Quarterly Review of Biophysics, 2003, 36, pp307-340) teaches that prediction of protein function from sequence and structure is difficult problem, because homologous proteins often have different function. A fundamental problem is that function is in many cases an ill-defined concept (see Abstract in particular). Even in situations where there is some confidence of a similar overall structure between two proteins, only experimental research can confirm the artisan's best guess as to the function of the structurally related protein (see in particular "Abstract" and Box 2). Finally, even single amino acid differences can result in drastically altered functions between two proteins. For example, Metzler et al. (Nature Structural Biol. 1997; 4:527-531) show that any of a variety of single amino acid changes can alter or abolish the ability of CTLA4 to interact with its ligands CD80 and CD86 (e.g., summarized in Table 2). Thus it is unpredictable if any functional activity will be shared by two polypeptides having less than 100% identity over the full length of their sequences.

In view of this unpredictability; the skilled artisan would not reasonably expect a polypeptide having anything less than 100% identity *over the full length of SEQ ID NO:2* to *share the same function* as the polypeptide of SEQ ID NO:2. Thus the recitation of percent identity language does not allow the skilled artisan to make and use any antibody that specifically binds to a polypeptide having an amino acid sequence at least 60 % identical to SEQ ID NO:2, claimed in claim 28 that can be used for purification and detection 7F4 protein of SEQ ID NO:2 or for antibody therapy of bone disorder commensurate in scope with the claimed invention without undue experimentation.

B. Similarly, the fact that two nucleic acid sequences will hybridize under moderate or stringent conditions does not in and of itself require that the two sequences share any functional activity. Thus the same observations apply to the recitation of "a polypeptide encoded by the first nucleic acid that hybridized under stringent conditions to a second nucleic acid consisting of SEQ ID NO:3" recited in claim 30 as were noted above with respect to "percent identity" language. Further, it was well known in the art at the time the invention was made that hybridization could occur between two sequence based upon short stretches of 100% identity. Thus a great deal of sequence variability *with respect to the full-length nucleic acid* is possible and in the absence of a clear recitation that the identity is over the full length of SEQ ID NO:3, the claim reads on subsequences and would be viewed by the skilled artisan as been even less likely to encode a polypeptide with the same function as polypeptide encoded by SEQ ID NO:2. Thus as for the

recitation of percent identity, hybridization language in the absence of limitations regarding the *sequence length over which the hybridization takes place*; does not allow the skilled artisan to make and use any antibody that specifically binds to a polypeptide encoded by the first nucleic acid that hybridized under stringent conditions to a second nucleic acid consisting of SEQ ID NO:3, recited in claim 30 for purification and detection 7F4 protein of SEQ ID NO:2 or for antibody therapy of bone disorder commensurate in scope with the instant claims without undue experimentation.

C. Also an issue is that claim 30 recited " an antibody that specifically binds to a polypeptide encoded by a first nucleic acid that hybridizes under stringent conditions to a second nucleic acid consisting of SEQ ID NO:3, wherein the polypeptide induces differentiation of an osteocyte". The specification disclosed that nucleic sequence of SEQ ID NO:3 encoded a 7F4 protein of SEQ ID NO:2 that induces differentiation of an osteocyte (page 3, lines 15-30 and page 6, lines 15-30 in particular). Nucleic acid hybridization is a process by which the DNA of a gene is detected by its base pairing with a **complementary** (antisense) sequence on another nucleic acid molecule. One cannot extrapolate the teachings of the specification to the scope of the claims because the claims are drawn to an antibody that specifically binds to the polypeptide that is encoded by a complementary (antisense) sequence of a nucleic acid. Said antisense sequence does not encoded the 7F4 protein of SEQ ID NO:2 and thus polypeptide encoded by antisense sequence can not induces differentiation of an osteocyte. The antisense sequence to the nucleic acid consisting of SEQ ID NO:3 has no open reading frame (ORF) for 7F4 polypeptide of SEQ ID NO:2. The resultant polypeptides do not have the biological properties representative of what is being claimed, and applicant has not enabled any of these types of polypeptides because it has not been shown that these polypeptides are capable of functioning as that which is being disclosed.

Thus, Applicant has not provided sufficient guidance to enable one skill in the art to use claimed antibody that specifically binds to a polypeptide having an amino acid sequence at least 60 % identical to SEQ ID NO:2, claimed in claim 28; or (ii) any antibody that specifically binds to a polypeptide encoded by the first nucleic acid that hybridized under stringent conditions to a second nucleic acid consisting of SEQ ID NO:3, recited in claim 30. in manner reasonably correlated with the scope of the claims. The scope of the claims must bear a reasonable correlation with the scope of enablement. *In re Fisher*, 166 USPQ 18(CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute.

In view of the quantity of experimentation necessary, the unpredictability of the art, the lack of sufficient guidance in the specification, the limited working examples, and the limited amount of direction provided given the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

13. Claims 28 and 30 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant is in possession of : an isolated antibody that specifically binds to a polypeptide consisting of SEQ ID NO:2.

Applicant is not in possession of : an antibody that specifically binds to a polypeptide having an amino acid sequence at least 60 % identical to SEQ ID NO:2, claimed in claim 28; or (ii) an antibody that specifically binds to a polypeptide encoded by the first nucleic acid that hybridized under stringent conditions to a second nucleic acid consisting of SEQ ID NO:3, recited in claim 30.

The claimed invention is drawn to a genus of antibody that recognize and specifically binds to any polypeptide having an amino acid sequence at least 60 % identical to SEQ ID NO:2, or (ii) to a polypeptide encoded by the first nucleic acid that hybridized under stringent conditions to a second nucleic acid consisting of SEQ ID NO:3 however, structural identifying characteristics of the genus are not disclosed. There is no evidence that there is any *per se* structure/function relationship between the disclosed an isolated antibody that specifically binds to a polypeptide consisting of SEQ ID NO:2 that can be used for purification and detection 7F4 protein of SEQ ID NO:2 or for antibody therapy of bone disorder and other that may be found using the claimed method. The specification does not disclosed any amino acid sequences of any polypeptide having an amino acid sequence at least 60 % identical to SEQ ID NO:2, or any polypeptide encoded by the first nucleic acid that hybridized under stringent conditions to a second nucleic acid consisting of SEQ ID NO:3, or amino-acid of claimed antibody, that can specifically bind to said polypeptide and can be used for purification and detection 7F4 protein of SEQ ID NO:2 or for antibody therapy of bone disorder. Moreover, it was well known in the art at the time the invention was made that hybridization could occur between two sequence based upon short stretches of 100% identity. Thus a great deal of sequence variability *with respect to the full-length nucleic acid* is possible and in the absence of a clear recitation that the identity is over the full length of SEQ ID NO:3, the claim 30 can reads on an antibody that can bind to a subsequences that would be viewed by the skilled artisan as been even less likely to encode a polypeptide with the same function as polypeptide encoded by SEQ ID NO:2.

Applicant has disclosed a limited number of species; therefore, the skilled artisan cannot envision all the contemplated amino acid sequence possibilities recited in the instant claims. Consequently, conception in either case cannot be achieved until a representative description of the structural and functional properties of the claimed invention has occurred, regardless of the complexity or simplicity of the method. Adequate written description requires more than a mere statement that it is part of the invention. The sequences themselves are required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993).

A description of a protein by functional language in the absence of a structure is not considered sufficient to show possession of the claimed invention. A description of what a material does i.e. antibody that bind to a polypeptide, wherein said polypeptide induces differentiation of an osteocyte, rather than of what it is, usually does not suffice. See Fiers, 984 F.2d at 1169-71, 25 USPQ2D at 1605-06. It is only a definition of a useful result rather than a definition of what achieves that result. Many species may achieve that result. The definition requirement of the patent statute requires a description of an invention, not an indication of a result that one might achieve if one made that invention. See *In re Wilder*, 736 /f.2d 1516, 1521, 22 USPQ 369, 372-73 (Fed. Cir. 1984) affirming the rejection because the specification does "little more than outline[e] goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate.") Accordingly, naming a type of material generally known to exist, in the absence of knowledge as to what the material consists of (e.g. structural feature), is not a description of that material.

The Examiner notes that the claimed invention which is drawn to a genus of antibody sequences may be adequately described if there is a (1) sufficient description of a representative number of species, or (2) by disclosure of relevant, identifying characteristics sufficient to describe the claimed invention in such full, clear, concise and exact terms that a skilled artisan would recognize applicant was in possession of the claimed invention. To satisfy the disclosure of a "representative number of species" will depend on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed. "Relevant, identifying characteristics" include structure or other physical and /or chemical properties, functional characteristics coupled with a known or disclosed correlation between function and structure, or a combination of such identifying characteristics sufficient to show the applicant was in possession of the claimed genus.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the written description inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.). Consequently, Applicant was not in possession of the instant claimed invention. See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.

Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

14. No claim is allowed.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michail Belyavskyi whose telephone number is 571/272-0840. The examiner can normally be reached Monday through Friday from 9:00 AM to 5:30 PM. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on 571/272-0841.

The fax number for the organization where this application or proceeding is assigned is 571/273-8300

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Michail Belyavskyi, Ph.D.
Patent Examiner
Technology Center 1600
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